Chapter 6
HIV and Liver Disease

A1a. Develop improved regimens of HAV and HBV vaccination. In a recent NIH-sponsored Pediatric AIDS Clinical Trials Group study, administration of a third dose of HAV vaccine gave higher levels of protective antibodies in children than with fewer doses (Weinberg A. *J Infect Dis* 2006;193:302). A study of immunologic boosting of HBV vaccine responses using GM-CSF in seronegative HIV-infected persons is in progress in an NIH-sponsored Adult AIDS Clinical Trials Group (AACTG) study. (10%)

A1b. Define short- and long-term safety and efficacy of peginterferon and ribavirin in different subpopulations of patients with HIV-HCV co-infection. Four large pivotal studies of peginterferon and ribavirin use in HIV/HCV co-infected persons were published in 2004. Additional studies are needed to define response rates in subpopulations of HIV/HCV co-infected patients. An ongoing AACTG study is evaluating whether concurrent HAART therapy improves response rates to peginterferon and ribavirin. (0%)

A2. Define safety and efficacy of peginterferon therapy for acute hepatitis C in HIV co-infection. A retrospective analysis of 11 HIV-infected patients with acute hepatitis C who were treated with interferon, with or without ribavirin, reported that 10 had a sustained virologic response (Vogel M. *J Viral Hepat* 2005:12:207). Better definition of the optimal time of starting, dose of peginterferon and ribavirin, and duration of therapy is needed. (20%)

A3. Define effects of HIV infection on the liver, including on different populations of liver cells. Little direct evidence exists of how HIV affects the liver; however, research is active in this area. A recent study reported no differences in CD8+ and CD4+ lymphocyte responses in the liver of co-infected vs HCV-mono-infected persons (Alatrakchi N. *J Infect Dis* 2005;191:702). HIV/HCV co-infected patients had more intrahepatic Fas expression than mono-infected persons (Macias J. *J Infect Dis* 2005;192:1566). (10%)

B1a. Define whether long-term peginterferon slows progression of disease in chronic hepatitis C with HIV co-infection. The AACTG is sponsoring a clinical trial entitled "Suppressive Long-term Antiviral Management of Hepatitis C Virus (HCV) in HIV-1 Co-infected Subjects" to evaluate the safety and efficacy of long-term antiviral treatment. (10%)

B1b. Define prevalence, etiology, and severity of different liver diseases in different cohorts of HIV-infected patients. Liver disease was the second leading cause of death in a large cohort of HIV-infected persons from Australia, Europe, and the US. Hepatic steatosis was present in 40 to 56 percent of HCV/HIV-co-infected persons and was associated with Caucasian race, increased body weight, lipodystrophy and stavudine use (Sulkowski MS. *AIDS* 2005;19:585; Marks KM. *J Infect Dis* 2005;192:1943). The role of antiretroviral

therapy and alcohol intake in the progression of liver disease in HIV-infected persons remains controversial. (20%)

B2a. Elucidate mechanisms by which HIV infection accelerates fibrosis and disease progression in HBV and HCV infection. The mechanisms by which HIV infection accelerates progression of liver fibrosis remain largely unknown and are the focus of several ongoing studies. (0%)

B2b. Define factors that lead to reactivation of HBV in HIV co-infection and develop means of prevention. The causes of sudden worsening or reactivation of hepatitis B in HIV co-infected persons include (1) loss of anti-HBV due to progressive immune deficiency, (2) stopping antiretroviral drugs with anti-HBV activity, and (3) development (or selection) of HBV resistance mutations. Activity against lamivudine-resistant HBV is excellent for tenofovir and moderate for entecavir, but their optimal use needs to be better defined. (20%)

B3. Develop noninvasive means of detecting early hepatic mitochondrial dysfunction. New methods of detecting early mitochondrial dysfunction have not been reported. The NIH has encouraged research in this area through its initiatives on "Noninvasive Methods for Diagnosis and Progression" (PA-04-088) and "Development of Disease Biomarkers" (PA-05-098). (0%)

C1a. Develop optimal therapeutic regimens for chronic hepatitis B in different stages and patterns of disease in HIV-co-infected patients. In 2005, a European Consensus Panel recommended tenofovir-emtricitabine as the optimal treatment for hepatitis B in HIV-infected persons (Soriano V. *AIDS* 2005;19: 221). The long-term efficacy of this approach needs further definition and studies of newer agents (telbivudine, clevudine, entecavir) are in order. (20%)

C1b. Define safety and efficacy of new agents for therapy of hepatitis C in HIV co-infection. Combination therapy using peginterferon and ribavirin received FDA approval for use in HIV/HCV co-infected persons in 2005 (3 years after approval for HCV mono-infected patients). Although several new compounds with activity against HCV have been developed and are moving through clinical trial phases, HIV/HCV cohorts have not been included in early testing. (0%)

C2. Develop noninvasive means of assessing liver disease stage and activity in HIV-infected persons. During 2005, noninvasive methods for assessing the stage of liver disease were reported in HIV/HCV co-infected persons, including algorithms based on the serum testing and liver elastography, which yield reasonable correlations separating minimal from severe fibrosis. (20%)

C3a. Develop *in vitro* or *in vivo* models of HIV-HCV and HIV-HBV co-infection. *In vitro* systems of HCV replication were recently developed. Additional research is needed to build upon these systems in order to develop *in vitro* models of HIV/HCV or HIV/HBV co-infection. (0%)

C3b. Develop means to reliably attribute causality of drug-induced liver disease in HIV-infected persons. Collaborations between the Drug-Induced Liver Injury Network (DILIN) and the AACTG have been established to develop common instruments for assessing drug-induced liver disease. The complexity of liver

disease and the use of multiple drugs for treatment of HIV-infected persons makes assignment of causality of liver injury a challenge. (0%)

Figure 8. Estimated Progress on HIV and Liver Disease Research Goals, 2005 (Year 1)